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FILE 'REGISTRY' ENTERED AT 15:45:33 ON 15 MAY 2002

L1 E AMLODIPINE/CN  
1 SEA AMLODIPINE/CN  
E "(R)-(+) -AMLODIPINE"/CN  
L2 1 SEA "(R)-(+) -AMLODIPINE"/CN  
E "(L)-(-) -AMLODIPINE"/CN  
E "(S)-(-) -AMLODIPINE"/CN  
L3 1 SEA "(S)-(-) -AMLODIPINE"/CN  
L4 3 SEA L1 OR L2 OR L3

FILE 'HCAPLUS' ENTERED AT 15:47:21 ON 15 MAY 2002

L5 10 SEA (L4 OR AMLODIPINE) AND CARRIER

L5 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:122825 HCAPLUS

DOCUMENT NUMBER: 136:172796

TITLE: Composition for transdermal and/or transmucosal  
administration of active compounds that ensures  
adequate therapeutic levels

INVENTOR(S): Carrara, Dario; Porto, Gabriel; Rodriguez, Jorge

PATENT ASSIGNEE(S): Antares Pharma IPL A.-G., Switz.

SOURCE: PCT Int. Appl., 83 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002011768	A1	20020214	WO 2001-EP9007	20010803
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: WO 2000-EP7533 A 20000803

OTHER SOURCE(S): MARPAT 136:172796

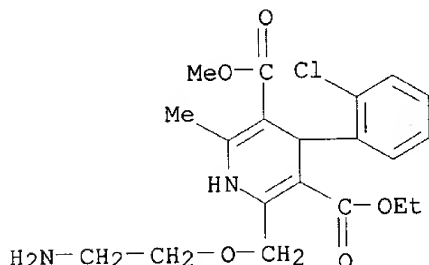
AB The present invention refers to a pharmaceutical compn. suitable for the transdermal or transmucosal administration of one or more active agents, in form of a gel or a soln., comprising as a permeation enhancers a combination of: a) satd. fatty alc. of formula  $\text{Me}(\text{CH}_2)_n\text{CH}_2\text{OH}$  or satd. fatty acid  $\text{Me}(\text{CH}_2)_n\text{CH}_2\text{COOH}$  wherein  $n = 8-12$ , most preferably 10, or unsatd. fatty alc. or fatty acid:  $\text{Me}[\text{CnH}_2(n-1)]\text{OH}$  or  $\text{Me}[\text{CnH}_2(n-1)]\text{COOH}$  wherein  $n = 8-22$ , b) a ternary vehicle or **carrier** consisting of a C1-C4 alkanol, a polyalc. in particular propylene glycol and water, c) optionally also a monoalkyl ether of diethylene glycol. A gel was prepd. contg. testosterone, lauryl alc., Transcutol P, propylene glycol, ethanol, distd. water, Carbopol 980, triethanolamine, and di-Na EDTA.

IT **88150-42-9, Amlodipine**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(compn. for transdermal and/or transmucosal administration of active compds. that ensures adequate therapeutic levels)

RN 88150-42-9 HCAPLUS  
 CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

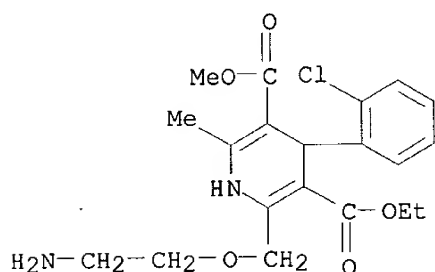
L5 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2002:71857 HCAPLUS  
 DOCUMENT NUMBER: 136:139826  
 TITLE: Selective cyclooxygenase-2 inhibitors and vasomodulator compounds for generalized pain and headache pain  
 INVENTOR(S): Hassan, Fred; Forbes, James C.  
 PATENT ASSIGNEE(S): Pharmacia Corporation, USA  
 SOURCE: PCT Int. Appl., 218 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002005799	A2	20020124	WO 2001-US22103	20010713
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 2000-218101P	P 20000713
			US 2001-284248P	P 20010417
			US 2001-296196P	P 20010606

OTHER SOURCE(S): MARPAT 136:139826

AB A therapeutic combination useful in the treatment, amelioration, prevention, or delay of pain comprising a high energy form of a selective cyclooxygenase-2 inhibitor, a vasomodulator, and a pharmaceutically acceptable excipient, **carrier**, or diluent, the cyclooxygenase-2 inhibitor and vasomodulator each being present in an amt. effective to contribute to the treatment, prevention, or delay of pain. Thus, capsules contained celecoxib 200, Labrasol 280, diethylene glycol monoethyl ether 280, and propylene glycol laurate 140/capsule.

IT **88150-42-9, Amlodipine**  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (cyclooxygenase-2 inhibitors and vasomodulators for generalized pain  
 and headache pain treatment)  
 RN 88150-42-9 HCAPLUS  
 CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-  
 chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA  
 INDEX NAME)



L5 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2001:396644 HCAPLUS  
 DOCUMENT NUMBER: 135:24671  
 TITLE: Solid carriers for improved delivery of active  
 ingredients in pharmaceutical compositions  
 INVENTOR(S): Patel, Manesh V.; Chen, Feng-jing  
 PATENT ASSIGNEE(S): Lipocine, Inc., USA  
 SOURCE: PCT Int. Appl., 107 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001037808	A1	20010531	WO 2000-US32255	20001122
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG US 6248363 B1 20010619 US 1999-447690 19991123				

PRIORITY APPLN. INFO.: US 1999-447690 A 19991123

AB The present invention provides solid pharmaceutical compns. for improved  
 delivery of a wide variety of pharmaceutical active ingredients contained  
 therein or sep. administered. In one embodiment, the solid pharmaceutical  
 compn. includes a solid **carrier**, the solid **carrier**  
 including a substrate and an encapsulation coat on the substrate. The  
 encapsulation coat can include different combinations of pharmaceutical  
 active ingredients, hydrophilic surfactant, lipophilic surfactants and  
 triglycerides. In another embodiment, the solid pharmaceutical compn.  
 includes a solid **carrier**, the solid **carrier** being

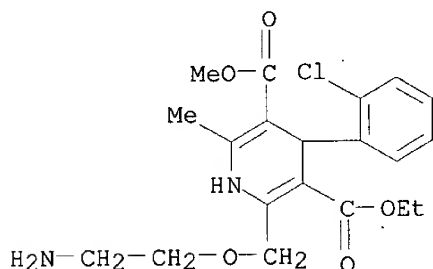
formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides. The compns. of the present invention can be used for improved delivery of hydrophilic or hydrophobic pharmaceutical active ingredients, such as drugs, nutritionals, cosmeceuticals and diagnostic agents. A compn. contained glyburide 1, PEG 40 stearate 33, glycerol monolaurate 17, and nonpareil seed 80 g.

IT **88150-42-9, Amlodipine**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(solid carriers for improved delivery of active ingredients in pharmaceutical compns.)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:338762 HCAPLUS

DOCUMENT NUMBER: 134:362292

TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile

INVENTOR(S): Farr, Spencer

PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA

SOURCE: PCT Int. Appl., 222 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 1999-165398P	P 19991105
			US 2000-196571P	P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to det. the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes assocd. with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes assocd. with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes assocd. with hypersensitivity. The expression of the genes predetd. to be assocd. with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and app. useful for identifying hypersensitivity in a subject are also disclosed.

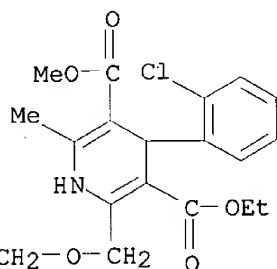
IT **88150-42-9, Amlodipine**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:195203 HCAPLUS

DOCUMENT NUMBER: 134:202702

TITLE: Valsartan-calcium channel blocker combination composition and treatment for cardiovascular and other conditions

INVENTOR(S): Webb, Randy Lee; de Gasparo, Marc

PATENT ASSIGNEE(S): Novartis A.-G., Switz.

SOURCE: U.S., 5 pp.  
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 6204281 B1 20010320 US 1999-349654 19990708  
US 2001049384 A1 20011206 US 2001-757413 20010109  
PRIORITY APPLN. INFO.: US 1998-155262P P 19980710  
US 1999-349654 A3 19990708

AB A method is provided for the treatment or prevention of a condition or disease selected from hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, myocardial infarction and its sequelae, supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, atherosclerosis, angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, hypertension in patients with NIDDM, secondary aldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), and stroke, comprising administering a therapeutically effective amt. of combination of (i) the AT1 antagonist valsartan, or a pharmaceutically acceptable salt thereof, and (ii) a calcium channel blocker, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable **carrier** to a mammal in need of such treatment. A pharmaceutical combination compn. is also provided.

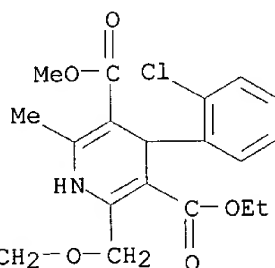
IT **88150-42-9, Amlodipine**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(valsartan-calcium channel blocker combination compn. and treatment for cardiovascular and other conditions)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT:

13

THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:725436 HCAPLUS

DOCUMENT NUMBER: 133:301171

TITLE: Compositions and methods for improved delivery of ionizable hydrophobic therapeutic agents

INVENTOR(S): Chen, Feng-jing; Patel, Manesh V.

PATENT ASSIGNEE(S): Lipocine, Inc., USA

SOURCE: PCT Int. Appl., 99 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059475	A1	20001012	WO 2000-US7342	20000316
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6383471	B1	20020507	US 1999-287043	19990406
EP 1165048	A1	20020102	EP 2000-916547	20000316
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1999-287043 A 19990406  
 WO 2000-US7342 W 20000316

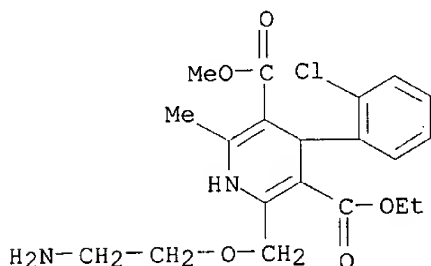
AB The present invention is directed to a pharmaceutical compn. including a hydrophobic therapeutic agent having at least one ionizable functional group, and a **carrier**. The **carrier** includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents. The invention further relates to a method of prepg. such compns. by providing a compn. of an ionizable hydrophobic therapeutic agent, an ionizing agent, and a surfactant, and neutralizing a portion of the ionizing agent with a neutralizing agent. The compns. of the invention are particularly suitable for use in oral dosage forms. A **carrier** contg. concd. phosphoric acid 0.025, Tween-20 0.3, Arlacel 186 0.2, sodium taurocholate 0.15, propylene glycol 0.3 g was formulated. Itraconazole was included in the **carrier** at 30 mg/mL for testing the stability of the itraconazole soln. upon diln. in simulated gastric fluid.

IT 88150-42-9, Amlodipine

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (pharmaceutical compns. contg. hydrophobic therapeutic agents and carriers contg. ionizing agents and surfactants and triglycerides)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT:

3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:608551 HCAPLUS

DOCUMENT NUMBER: 133:213151

TITLE: Pharmaceutical compositions and methods for improved delivery of hydrophobic therapeutic agents

INVENTOR(S): Patel, Manesh V.; Chen, Feng-Jing

PATENT ASSIGNEE(S): Lipocine, Inc., USA

SOURCE: PCT Int. Appl., 98 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

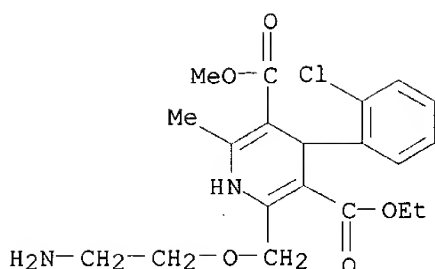
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050007	A1	20000831	WO 2000-US165	20000105
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 6294192	B1	20010925	US 1999-258654	19990226
EP 1158959	A1	20011205	EP 2000-901394	20000105
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
US 2002012680	A1	20020131	US 2001-898553	20010702
PRIORITY APPLN. INFO.:			US 1999-258654	A 19990226
			WO 2000-US165	W 20000105
AB	The present invention relates to triglyceride-free pharmaceutical compns. for delivery of hydrophobic therapeutic agents. Compns. of the present invention include a hydrophobic therapeutic agent and a <b>carrier</b> , where the <b>carrier</b> is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon diln. with an aq. solvent, the compn. forms a clear, aq. dispersion of the surfactants contg. the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compns. A pharmaceutical compn. contained cyclosporin 0.14, Cremophor RH-40 0.41, Arlacell186 0.29, sodium taurocholate 0.26, and propylene glycol 0.46 mg.			
IT	<b>88150-42-9, Amlodipine</b> RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (pharmaceutical compns. and methods for improved delivery of hydrophobic therapeutic agents)			
RN	88150-42-9 HCAPLUS			
CN	3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)			





REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:531583 HCAPLUS

DOCUMENT NUMBER: 133:140256

TITLE: Controlled release pharmaceutical dosage forms containing polymers

INVENTOR(S): Ayer, Atul D.; Lam, Andrew; Magruder, Judy A.; Hamel, Lawrence G.; Wong, Patrick S. L.

PATENT ASSIGNEE(S): Alza Corporation, USA

SOURCE: U.S., 15 pp.

CODEN: USXXAM

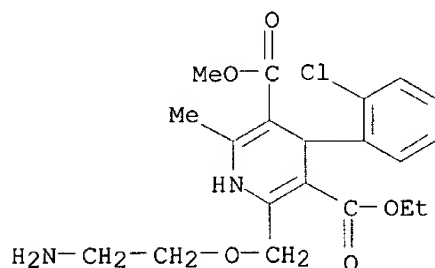
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	US 6096339	A	20000801	US 1997-826642	19970404
AB	The invention disclosed pertains to a controlled-release dosage form comprising a drug and a pharmaceutical <b>carrier</b> (a hydrophilic polymer) of the right particle size. The drug has a particle size of <150 .mu.m and the polymer has the size <250 .mu.m.				
IT	<b>88150-42-9, Amlodipine</b> RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (controlled release pharmaceutical dosage forms contg. polymers)				
RN	88150-42-9 HCAPLUS				
CN	3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)				



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:109766 HCAPLUS

DOCUMENT NUMBER: 133:37955

TITLE: Comparative effects of different dihydropyridines on the expression of adhesion molecules induced by TNF-.alpha. on endothelial cells

AUTHOR(S): Cominacini, Luciano; Pasini, Anna Fratta; Pastorino, Antonio M.; Garbin, Ulisse; Davoli, Anna; Rigoni, Anna; Campagnola, Mario; Tosetti, Maria L.; Rossato, Paolo; Gaviraghi, Giovanni

CORPORATE SOURCE: Department of Internal and Surgical Sciences, University of Verona, Verona, Italy

SOURCE: Journal of Hypertension (1999), 17(12, Pt. 2), 1837-1841

CODEN: JOHYD3; ISSN: 0263-6352

PUBLISHER: Lippincott Williams &amp; Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Lacidipine has already been demonstrated to reduce the expression of some adhesion mols. induced by pro-oxidant signals on endothelial cells. In order to verify if this effect is a peculiarity of this mol., or belongs to other dihydropyridinic compds. (DHPs), the activity of lacidipine was compared with that of lercanidipine, **amlodipine**, nimodipine and nifedipine. The compds. were incorporated in human umbilical vein endothelial cells (HUVECs) using native low-d. lipoprotein as a **carrier**. The drug concns. in HUVECs were measured by mass spectrometry. Human recombinant tumor necrosis factor-.alpha. was then incubated with HUVECs for 7 h at 37.degree. for adhesion mol. expression. The cellular amt. of lacidipine, lercanidipine and **amlodipine** was similar, while nimodipine and nifedipine were almost undetectable or undetectable, resp. Lacidipine, at any concn., detd. a dose-dependent significant decrease of the expression of intercellular adhesion mol.-1 (ICAM-1), vascular cell adhesion mol.-1 (VCAM-1) and E-selectin. Lercanidipine and **amlodipine** detd. variable decreases of adhesion mols. at the intermediate and highest concns. Nimodipine and nifedipine detd. no effect on ICAM-1, VCAM-1 and E-selectin. The lowest IC50, i.e. the concn. detg. the 50% redn. of ICAM-1, VCAM-1 and E-selectin expression was obtained with lacidipine for all the adhesion mols. considered. It is concluded that the effect of the DHPs used in this study on adhesion mol. expression is detd. first by their lipophilicity and then by their intrinsic antioxidant activity.

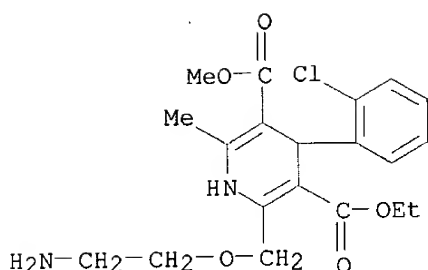
IT 88150-42-9, **Amlodipine**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of different dihydropyridine calcium antagonists on expression of adhesion mols. induced by TNF-.alpha. on endothelial cells)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2000:53366 HCAPLUS  
 DOCUMENT NUMBER: 132:88204  
 TITLE: Method of treatment and pharmaceutical composition using valsartan-calcium channel blocker combination  
 INVENTOR(S): De Gasparo, Marc; Webb, Randy Lee  
 PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.  
 SOURCE: PCT Int. Appl., 14 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000002543	A2	20000120	WO 1999-EP4842	19990709
WO 2000002543	A3	20000629		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9950349	A1	20000201	AU 1999-50349	19990709
BR 9912021	A	20010403	BR 1999-12021	19990709
EP 1096932	A2	20010509	EP 1999-934647	19990709
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001000113	A	20010309	NO 2001-113	20010108
PRIORITY APPLN. INFO.: US 1998-113893 A 19980710				
WO 1999-EP4842 W 19990709				

AB A method is provided for the treatment or prevention of a condition or disease selected from hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, myocardial infarction and its sequelae supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, atherosclerosis, angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, hypertension in patients with NIDDM, secondary aldosteronism, primary and secondary

pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), and stroke, comprising administering a therapeutically effective amt. of combination of (i) the AT1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a calcium channel blocker or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable **carrier** to a mammal in need of such treatment. A corresponding pharmaceutical combination compn. is also provided.

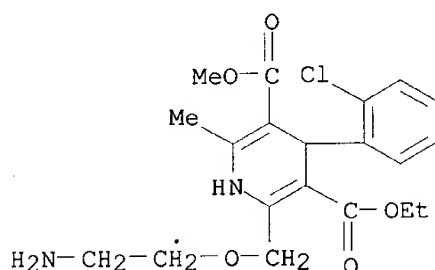
IT **88150-42-9, Amlodipine**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(valsartan-calcium channel blocker pharmaceutical combination)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO' ENTERED AT  
15:50:34 ON 15 MAY 2002

SET COST OFF

L6

22 SEA L5

=> d 16 ibib abs 1-22

L6 ANSWER 1 OF 22

MEDLINE

ACCESSION NUMBER: 2001678283 MEDLINE

DOCUMENT NUMBER: 21580729 PubMed ID: 11724204

TITLE: The effects of dihydropyridine and phenylalkylamine calcium antagonist classes on autonomic function in hypertension: the VAMPHYRE study.

AUTHOR: Lefrandt J D; Heitmann J; Sevre K; Castellano M; Hausberg M; Fallon M; Fluckiger L; Urbigkeit A; Rostrup M; Agabiti-Rosei E; Rahn K H; Murphy M; Zannad F; de Kam P J; van Roon A M; Smit A J

CORPORATE SOURCE: University Hospital of Groningen, The Netherlands..  
j.d.lefrandt@int.azg.nl

SOURCE: AMERICAN JOURNAL OF HYPERTENSION, (2001 Nov) 14 (11 Pt 1)  
1083-9.

Journal code: 8803676. ISSN: 0895-7061.

PUB. COUNTRY: United States  
(CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)  
(MULTICENTER STUDY)  
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200203  
ENTRY DATE: Entered STN: 20011129  
Last Updated on STN: 20020307  
Entered Medline: 20020306

AB The aim of the present study was to compare the effects of a long-acting dihydropyridine (**amlodipine**) and a nondihydropyridine (verapamil) on autonomic function in patients with mild to moderate hypertension. A total of 145 patients with a diastolic blood pressure (BP) between 95 and 110 mm Hg received 8 weeks of verapamil sustained release (240 mg) and **amlodipine** (5 mg) in a prospective randomized, double blind, cross-over study, both after 4 weeks of placebo. The 24-h autonomic balance was measured by analysis of 24-h heart rate variability and short-term autonomic control of BP by baroreflex sensitivity measurements. Plasma norepinephrine was sampled at rest. Blood pressure was equally reduced from 153/100 mm Hg to 139/91 mm Hg with verapamil and 138/91 mm Hg with **amlodipine**,  $P = .50/.59$ . The low- to high-frequency ratio (LF/HF), reflecting sympathovagal balance, was higher with **amlodipine** than with verapamil ( $4.66$  v  $4.10$ ;  $P = .001$ ). Baroreflex function was improved by both treatments; however, baroreflex sensitivity (BRS) was significantly higher with verapamil than with **amlodipine** ( $8.47$  v  $8.06$  msec/mm Hg;  $P = .01$ ). Plasma norepinephrine (NE) level was higher with **amlodipine** than with verapamil ( $1.59$  v  $1.32$  nmol/L;  $P < .0001$ ). **Amlodipine** induces a shift in sympathovagal balance, as measured by heart rate variability indices and plasma NE, toward sympathetic predominance compared with vagal predominance with verapamil. Short-term autonomic control of BP, as assessed by BRS, is more effectively improved by verapamil than by **amlodipine**. These contrasting effects on autonomic function suggest that the nondihydropyridine calcium antagonist verapamil may have additional beneficial effects beyond lowering BP compared with the dihydropyridine **amlodipine**.

L6 ANSWER 2 OF 22 MEDLINE

ACCESSION NUMBER: 2000166643 MEDLINE

DOCUMENT NUMBER: 20166643 PubMed ID: 10703877

TITLE: Comparative effects of different dihydropyridines on the expression of adhesion molecules induced by TNF-alpha on endothelial cells.

AUTHOR: Cominacini L; Pasini A F; Pastorino A M; Garbin U; Davoli A; Rigoni A; Campagnola M; Tosetti M L; Rossato P; Gaviraghi G

CORPORATE SOURCE: Department of Internal and Surgical Sciences, University of Verona, Italy.. comina@medicinad.univr.it

SOURCE: JOURNAL OF HYPERTENSION, (1999 Dec) 17 (12 Pt 2) 1837-41.  
Journal code: IEW; 8306882. ISSN: 0263-6352.

PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000327  
Last Updated on STN: 20000327  
Entered Medline: 20000316

AB OBJECTIVE: Lacidipine has already been demonstrated to reduce the expression of some adhesion molecules induced by pro-oxidant signals on

endothelial cells. In order to verify if this effect is a peculiarity of this molecule, or belongs to other dihydropyridinic compounds (DHPs), the activity of lacidipine was compared with that of lercanidipine, **amlodipine**, nimodipine and nifedipine. DESIGN AND METHODS: The compounds were incorporated in human umbilical vein endothelial cells (HUVECs) using native low-density lipoprotein as a **carrier**. The drug concentrations in HUVECs were measured by mass spectrometry. Human recombinant tumour necrosis factor- $\alpha$  was then incubated with HUVECs for 7 h at 37 degrees C for adhesion molecule expression. RESULTS: The cellular amount of lacidipine, lercanidipine and **amlodipine** was similar, while nimodipine and nifedipine were almost undetectable or undetectable, respectively. Lacidipine, at any concentration, determined a dose-dependent significant decrease of the expression of intercellular adhesion molecule-1 (ICAM-1) ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) VCAM-1 and E-selectin ( $P < 0.01$ ). Lercanidipine and **amlodipine** determined variable decreases of adhesion molecules at the intermediate and highest concentrations. Nimodipine and nifedipine determined no effect on ICAM-1, VCAM-1 and E-selectin. The lowest IC50, i.e. the concentration determining the 50% reduction of ICAM-1, VCAM-1 and E-selectin expression was obtained with lacidipine for all the adhesion molecules considered ( $P < 0.01$ ). CONCLUSIONS: It is concluded that the effect of the DHPs used in this study on adhesion molecule expression is determined first by their lipophilicity and then by their intrinsic antioxidant activity.

L6 ANSWER 3 OF 22 MEDLINE  
 ACCESSION NUMBER: 96021088 MEDLINE  
 DOCUMENT NUMBER: 96021088 PubMed ID: 7575651  
 TITLE: The low-affinity dihydropyridine receptor and  $\text{Na}^+/\text{Ca}^{2+}$  exchanger are associated in adrenal medullary mitochondria.  
 AUTHOR: Palmero M; Gutierrez L M; Hidalgo M J; Reig J A; Ballesta J J; Viniegra S  
 CORPORATE SOURCE: Departamento de Neuroquimica, Universidad de Alicante, Spain.  
 SOURCE: BIOCHEMICAL PHARMACOLOGY, (1995 Sep 7) 50 (6) 879-83.  
 Journal code: 9Z4; 0101032. ISSN: 0006-2952.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199510  
 ENTRY DATE: Entered STN: 19951227  
 Last Updated on STN: 20000303  
 Entered Medline: 19951031

AB The effect of  $\text{Ca}^{2+}$  channel-acting drugs on bovine adrenal mitochondria  $\text{Ca}^{2+}$  movements was investigated. Mitochondrial  $\text{Ca}^{2+}$  uptake is performed by an energy-driven  $\text{Ca}^{2+}$  uniporter with a  $K_m$  of  $20.9 \pm 3.2$   $\mu\text{M}$  and  $V_{\text{max}}$  of  $148.1 \pm 7.2$   $\text{nmol } 45\text{Ca}^{2+} \text{ min}^{-1} \text{ mg}^{-1}$ .  $\text{Ca}^{2+}$  release is performed through an  $\text{Na}^+/\text{Ca}^{2+}$  antiporter with a  $K_m$  for  $\text{Na}^+$  of  $4.2 \pm 0.5$   $\text{mM}$ , a  $V_{\text{max}}$  of  $7.5 \pm 0.4$   $\text{nmol } 45\text{Ca}^{2+} \text{ min}^{-1} \text{ mg}^{-1}$ , and a Hill coefficient of  $1.4 \pm 0.2$ .  $\text{Ca}^{2+}$  efflux through the mitochondrial  $\text{Na}^+/\text{Ca}^{2+}$  exchanger was inhibited by several dihydropyridines (nitrendipine, felodipine, nimodipine, (+)isradipine) and by the benzothiazepine diltiazem with similar potencies. In contrast, neither CGP 28392, Bay-K-8644, **amlodipine**, nor verapamil had any effect on  $\text{Ca}^{2+}$  efflux. Nitrendipine at 20  $\mu\text{M}$  modified neither the  $K_m$  nor the Hill coefficient for  $\text{Na}^+$ , whereas the  $V_{\text{max}}$  was reduced to  $2.9$   $\text{nmol } 45\text{Ca}^{2+} \text{ min}^{-1} \text{ mg}^{-1}$ , thus demonstrating noncompetitive modulation of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger. None of the  $\text{Ca}^{2+}$  channel-acting drugs assayed at 100  $\mu\text{M}$  affected  $\text{Ca}^{2+}$  influx through the uniporter.  $\text{Ca}^{2+}$  channel blockers inhibited the  $\text{Na}^+/\text{Ca}^{2+}$  antiporter and

displaced the specific binding of [3H]nitrendipine to intact mitochondria with Ki values similar to the IC50s obtained for the inhibition of the Ca2+ efflux. Ca2+ channel-acting drugs that did not inhibit the Na+/Ca2+ exchanger (**amlodipine**, CGP 28392, Bay-K-9644, and verapamil, at concentrations of 100 microM or higher) had no effect on [3H]nitrendipine binding. These results suggest that the adrenomedullary mitochondrial dihydropyridine receptor is associated with the Na+/Ca2+ exchanger.

L6 ANSWER 4 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:121779 BIOSIS

DOCUMENT NUMBER: PREV200000121779

TITLE: Comparative effects of different dihydropyridines on the expression of adhesion molecules induced by TNF-alpha on endothelial cells.

AUTHOR(S): Cominacini, Luciano (1); Pasini, Anna Fratta; Pastorino, Antonio M.; Garbin, Ulisse; Davoli, Anna; Rigoni, Anna; Campagnola, Mario; Tosetti, Maria L.; Rossato, Paolo; Gaviraghi, Giovanni

CORPORATE SOURCE: (1) Istituto di Semeiotica e Nefrologia Medica, Ospedale Policlinico, 37134, Verona Italy

SOURCE: Journal of Hypertension, (Dec., 1999) Vol. 17, No. 12 part 2, pp. 1837-1841.

ISSN: 0263-6352.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Objective Lacidipine has already been demonstrated to reduce the expression of some adhesion molecules induced by pro-oxidant signals on endothelial cells. In order to verify if this effect is a peculiarity of this molecule, or belongs to other dihydropyridinic compounds (DHPs), the activity of lacidipine was compared with that of lercanidipine, **amlodipine**, nimodipine and nifedipine. Design and methods The compounds were incorporated in human umbilical vein endothelial cells (HUVECs) using native low-density lipoprotein as a **carrier**. The drug concentrations in HUVECs were measured by mass spectrometry. Human recombinant tumour necrosis factor-alpha was then incubated with HUVECs for 7 h at 37degreeC for adhesion molecule expression. Results The cellular amount of lacidipine, lercanidipine and **amlodipine** was similar, while nimodipine and nifedipine were almost undetectable or undetectable, respectively. Lacidipine, at any concentration, determined a dose-dependent significant decrease of the expression of intercellular adhesion molecule-1 (ICAM-1) ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) VCAM-1 and E-selectin (P < 0.01). Lercanidipine and **amlodipine** determined variable decreases of adhesion molecules at the intermediate and highest concentrations. Nimodipine and nifedipine determined no effect on ICAM-1, VCAM-1 and E-selectin. The lowest IC50, i.e. the concentration determining the 50% reduction of ICAM-1, VCAM-1 and E-selectin expression was obtained with lacidipine for all the adhesion molecules considered (P < 0.01). Conclusions It is concluded that the effect of the DHPs used in this study on adhesion molecule expression is determined first by their lipophilicity and then by their intrinsic antioxidant activity.

L6 ANSWER 5 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001075021 EMBASE

TITLE: Chromatographic retention of drug molecules on immobilised liposomes prepared from egg phospholipids and from chemically pure phospholipids.

AUTHOR: Osterberg T.; Svensson M.; Lundahl P.

CORPORATE SOURCE: T. Osterberg, Preformulation Sciences, R and D Pharmacia

SOURCE: Corporation, SE-112 87 Stockholm, Sweden  
European Journal of Pharmaceutical Sciences, (2001) 12/4  
(427-439).  
Refs: 61  
ISSN: 0928-0987 CODEN: EPSCED  
PUBLISHER IDENT.: S 0928-0987(00)00183-4  
COUNTRY: Netherlands  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 029 Clinical Biochemistry  
037 Drug Literature Index  
039 Pharmacy  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB The partitioning of a chemically diverse set of drugs into liposomes was studied by immobilised liposome chromatography (ILC). For this purpose liposomes composed of (i) purified egg phospholipids (EPL), (ii) synthetic phosphatidylcholine (PC), (iii) PC-synthetic phosphatidylethanolamine (PE) 80:20 (mol/mol) and (iv) PC-synthetic phosphatidylserine (PS) 80:20 (mol/mol) were immobilised in gel beads by freeze-thawing. The drug partitioning was assessed from the retention volume, which was expressed as a capacity factor,  $K(s)$ , normalised with respect to the amount of immobilised phospholipid. The drug retention on EPL, PC and PC-PE liposomes was very similar, whereas the negatively charged PC-PS liposomes increased the retention of positively charged and decreased retention of negatively charged drugs. The partitioning of drugs on liposome columns ( $\log K(s)$ ) versus their octanol-water partitioning ( $\log P(oct)$ ) showed three separate rectilinear relationships, depending on the charge of the compound (neutral, positive, or negative). Statistical analysis (ANCOVA) proved that the lines had similar slopes. Repeated analysis of four reference compounds showed a low variation ( $<0.12$  log units) over time (about 250 days). A close relationship was observed between the drug retention in short EPL columns with a low content of phospholipids and the retention in longer standard EPL columns. The short 'quick screen bilayer columns' permit analysis of highly lipophilic compounds within 30 min and are thus applicable for medium-throughput screening in drug discovery settings. A very strong rectilinear relationship ( $r(2)=0.95$ ,  $n=13$ ) between  $\log K(s)$  (EPL) and published liposome partitioning data ( $\log D(mem)$ ) confirmed that the ILC drug retention reflects the drug partitioning into the lipid bilayers. A moderate to fair rectilinear relationship was observed between the normalised retention on PC, PC-PE and EPL liposomes ( $r(2)=0.79$ ,  $0.86$  and  $0.85$ , respectively,  $n=24$ ) and corresponding published  $\log k'(IAM)$  data obtained on immobilised artificial membrane (IAM) columns. Transport across Caco-2 cell monolayers ( $\log P(c)$ ) showed curvilinear relationships with  $\log K(s)$ ,  $\log k'(IAM)$ ,  $\log P(oct)$  and  $\log D(oct)$ . The drug fraction absorbed in humans showed a similar relationship to  $\log K(s)$  values as to surface plasmon resonance signals representing drug-liposome interaction (Danelian et al., 2000 J Med Chem, 43, 2083-2086). Copyright .COPYRGT. 2001 Elsevier Science B.V.

L6 ANSWER 6 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.  
ACCESSION NUMBER: 2000198330 EMBASE  
TITLE: Comparative effects of different dihydropyridines on the expression of adhesion molecules induced by TNF-.alpha. on endothelial cells.  
AUTHOR: Cominacini L.; Pasini A.F.; Pastorino A.M.; Garbin U.; Davoli A.; Rigoni A.; Campagnola M.; Tosetti M.L.; Rossato P.; Gaviraghi G.  
CORPORATE SOURCE: Dr. L. Cominacini, Ist. Semeiotica e Nefrologia Medica, Ospedale Policlinico, 37134 Verona, Italy.  
comina@medicinad.univr.it



SOURCE: Journal of Hypertension, (1999) 17/12 II (1837-1841).  
Refs: 42  
ISSN: 0263-6352 CODEN: JOHYD3  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; Conference Article  
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery  
030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AB Objective. Lacidipine has already been demonstrated to reduce the expression of some adhesion molecules induced by pro-oxidant signals on endothelial cells. In order to verify if this effect is a peculiarity of this molecule, or belongs to other dihydropyridinic compounds (DHPs), the activity of lacidipine was compared with that of lercanidipine, **amlodipine**, nimodipine and nifedipine. Design and methods. The compounds were incorporated in human umbilical vein endothelial cells (HUVECs) using native low-density lipoprotein as a **carrier**. The drug concentrations in HUVECs were measured by mass spectrometry. Human recombinant tumour necrosis factor- $\alpha$ . was then incubated with HUVECs for 7 h at 37.degree.C for adhesion molecule expression. Results. The cellular amount of lacidipine, lercanidipine and **amlodipine** was similar, while nimodipine and nifedipine were almost undetectable or undetectable, respectively. Lacidipine, at any concentration, determined a dose-dependent significant decrease of the expression of intercellular adhesion molecule-1 (ICAM-1) ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) VCAM-1 and E-selectin ( $P < 0.01$ ). Lercanidipine and **amlodipine** determined variable decreases of adhesion molecules at the intermediate and highest concentrations. Nimodipine and nifedipine determined no effect on ICAM-1, VCAM-1 and E-selectin. The lowest IC50, i.e. the concentration determining the 50% reduction of ICAM-1, VCAM-1 and E-selectin expression was obtained with lacidipine for all the adhesion molecules considered ( $P < 0.01$ ). Conclusions. It is concluded that the effect of the DHPs used in this study on adhesion molecule expression is determined first by their lipophilicity and then by their intrinsic antioxidant activity. (C) Lippincott Williams and Wilkins.

L6 ANSWER 7 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.  
ACCESSION NUMBER: 96052003 EMBASE  
DOCUMENT NUMBER: 1996052003  
TITLE:  $\alpha$ .2-Adrenoceptor activation increases calcium channel currents in single vascular smooth muscle cells isolated from human omental resistance arteries.  
AUTHOR: Hughes A.D.; Parkinson N.A.; Wijetunge S.  
CORPORATE SOURCE: Department of Clinical Pharmacology, Imperial Coll. of Science Technology, South Wharf Road, London W2 1NY, United Kingdom  
SOURCE: Journal of Vascular Research, (1996) 33/1 (25-31).  
ISSN: 1018-1172 CODEN: JVREE  
COUNTRY: Switzerland  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 002 Physiology  
030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AB Single cells were freshly isolated from human omental resistance arteries using an enzymatic dispersion technique. Calcium channel currents (I(Ba)) were recorded using whole cell voltage clamp techniques with Ba2+ as the charge **carrier**. BHT 933, a selective  $\alpha$ .2-adrenoceptor

agonist, increased I(Ba). The effect of BHT 933 was reversible following washout. The action of BHT 933 was blocked by yohimbine. Pretreatment of tissues with pertussis toxin for 18 h or inclusion of GDP-.beta.-S in the intracellular patch pipette solution also prevented the BHT 933-induced rise in I(Ba), but had no effect on I(Ba) in the absence of BHT 933. Activation of .alpha.2-adrenoceptors in human vascular smooth muscle cells increases I(Ba) by a mechanism involving a pertussis toxin-sensitive G protein.

L6 ANSWER 8 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
 ACCESSION NUMBER: 2002-218972 [28] WPIDS  
 DOC. NO. CPI: C2002-067112  
 TITLE: Therapeutic compositions comprising excess enantiomer of **amlodipine** useful for the treatment of a condition for which a vascular NO-releasing agent and an anti-hypertensive is indicated.  
 DERWENT CLASS: B02 B03  
 INVENTOR(S): CHAHWALA, S B; DODD, M G; HUMPHREY, M J  
 PATENT ASSIGNEE(S): (PFIZ) PFIZER INC; (PFIZ) PFIZER LTD; (CHAH-I) CHAHWALA S B; (DODD-I) DODD M G; (HUMP-I) HUMPHREY M J  
 COUNTRY COUNT: 29  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 1181932	A2	20020227	(200228)*	EN	8
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
CA 2355493	A1	20020223	(200228)	EN	
US 2002045648	A1	20020418	(200228)		
BR 2001003434	A	20020326	(200229)		

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1181932	A2	EP 2001-306940	20010815
CA 2355493	A1	CA 2001-2355493	20010821
US 2002045648	A1 Provisional	US 2000-237168P	20001002
		US 2001-930330	20010815
BR 2001003434	A	BR 2001-3434	20010817

PRIORITY APPLN. INFO: GB 2000-20842 20000823

AN 2002-218972 [28] WPIDS

AB EP 1181932 A UPAB: 20020502

NOVELTY - A pharmaceutical composition comprises the R(+) enantiomer of **amlodipine** or its salt, the S(-) enantiomer of **amlodipine** or its salt and an excipient, **carrier** or diluent. The enantiomers are present in a ratio by weight based on free base of R(+) enantiomer:S(-) enantiomer of greater than 1:1.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

- (1) preparation of the composition;
- (2) a pharmaceutical composition comprising an NO-releasing amount the R(+) enantiomer of **amlodipine** or its salt, an NO-inducing amount of an ACE inhibitor and an excipient, **carrier** or diluent;
- (3) a pharmaceutical composition comprising an NO-releasing amount the R(+) enantiomer of **amlodipine** or its salt, an NO-potentiating amount of an PDE5 inhibitor and an excipient, **carrier** or diluent.

ACTIVITY - Hypotensive.

MECHANISM OF ACTION - None given.

USE - The composition is used for the treatment of a condition for which a vascular NO-releasing agent and an anti-hypertensive is indicated.

ADVANTAGE - The compositions have both anti-hypertensive and additional cardiovascular properties derived respectively from their calcium channel blocking activity and their ability to release vascular nitric oxide.

Dwg.0/0

L6 ANSWER 9 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
 ACCESSION NUMBER: 2002-195775 [25] WPIDS  
 CROSS REFERENCE: 2002-195783 [14]  
 DOC. NO. CPI: C2002-060502  
 TITLE: Therapeutic combination for treatment, prevention or delay of pain (especially headache) comprises a high energy form of a selective cyclooxygenase-2 inhibitor, a vasomodulator and a **carrier**.  
 DERWENT CLASS: B02  
 INVENTOR(S): FORBES, J C; HASSAN, F  
 PATENT ASSIGNEE(S): (PHAA) PHARMACIA CORP  
 COUNTRY COUNT: 96  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002005799	A2	20020124	(200225)*	EN	217
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ					
NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK					
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR					
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU					
SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002005799	A2	WO 2001-US22103	20010713

PRIORITY APPLN. INFO: US 2001-296196P 20010606; US 2000-218101P  
 20000713; US 2001-284248P 20010417

AN 2002-195775 [25] WPIDS

CR 2002-195783 [14]

AB WO 200205799 A UPAB: 20020508

NOVELTY - Therapeutic combination for treatment, prevention or delay of pain comprises a high energy form of a selective cyclooxygenase-2 inhibitor, a vasomodulator and a **carrier**.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an orally deliverable comprising a selective cyclooxygenase-2 inhibitor in rapid release form, and a xanthine compound to treat headache pain; and

(2) a method of treatment of pain by administering a high energy form of a selective cyclooxygenase-2 inhibitor and a vasomodulator.

ACTIVITY - Analgesic; Antimigraine.

MECHANISM OF ACTION - Vasodilator; Vasoconstrictor; Cyclooxygenase-2 (COX-2) inhibitor; 5 HT1 receptor inhibitor.

The combined active agents bind to 5 HT1 receptors with an IC50 of at

least 250, 500, 750, 1000, 5000 or 10000 nM (claimed). In vivo bioavailability of a test composition (A) was compared to a Celebrex (RTM) capsule (B) and a celecoxib suspension (C). Cmax for (A), (B) and (C) was 2061, 621 and 804 ng/ml respectively. Tmax for (A), (B) and (C) was 1.03, 2.15 and 0.97 hours respectively. (A), (B) and (C) had AUC values of 7593, 5060 and 4892 ng/ml.hour respectively.

USE - To treat pain (especially headache pain (claimed)).

ADVANTAGE - The cyclooxygenase-2 inhibitor can be formulated in 2 fractions to provide instant effect (as solid particles) and in solution to provide sustained release.

Dwg.0/10

L6 ANSWER 10 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
ACCESSION NUMBER: 2002-138392 [18] WPIDS  
DOC. NO. CPI: C2002-042591  
TITLE: New pharmaceutical composition useful for the treatment of hypertension comprises deuterated S(-) **amlodipine** or its salt.  
DERWENT CLASS: B03  
INVENTOR(S): FOSTER, R T  
PATENT ASSIGNEE(S): (ISOT-N) ISOTECHNIKA INC  
COUNTRY COUNT: 1  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6333342	B1	20011225	(200218)*		10

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6333342	B1 Provisional	US 1998-107007P	19981104
		US 1999-433963	19991104

PRIORITY APPLN. INFO: US 1998-107007P 19981104; US 1999-433963 19991104

AN 2002-138392 [18] WPIDS

AB US 6333342 B UPAB: 20020319

NOVELTY - A pharmaceutical composition comprises deuterated pure S(-)isomer of **amlodipine** or its salt and a **carrier**.

DETAILED DESCRIPTION - A pharmaceutical composition comprises deuterated S(-)**amlodipine** of formula (I) or its salt and a **carrier**.

R and R1 = H or deuterium;

asterisk = chiral carbon.

At least one R and R1 are deuterium.

An INDEPENDENT CLAIM is also included for a compound of formula (I).

ACTIVITY - Hypotensive; antianginal; cerebroprotective; antiarrhythmic; nootropic; cardiant; virucide; thrombolytic; antiarteriosclerotic; antimigraine; vasotropic; neuroprotective; antiasthmatic; antiemetic; nephrotropic.

MECHANISM OF ACTION - Calcium channel blocker; calcium channel antagonist.

Test details are given but no results are given.

USE - In the treatment of calcium channel blocking therapy e.g. hypertension, angina, cerebral ischemia, cerebral disorders, arrhythmia, cardiac hypertrophy, heart failure, coronary vasospasm, myocardial infarction, renal impairment, viral infection, thrombosis,

atherosclerosis, peripheral vascular disease, migraine headache, restenosis following vascular surgery or injury or acute renal failure (all claimed); Alzheimer's dementia, memory impairment, retinal ischemia, asthma, bronchospasm, Raynaud's phenomenon or cognitive disorders.

ADVANTAGE - The composition avoids concomitant liability of adverse effects associated with administration of racemic **amlodipine**. The composition avoids toxicities and adverse effects of racemic **amlodipine**. The composition results in clearer dose-related definitions of efficacy and improves therapeutic index. The composition reduces the probability of occurrence of hypertension.

Dwg.0/0

L6 ANSWER 11 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
ACCESSION NUMBER: 2002-121537 [16] WPIDS  
CROSS REFERENCE: 2000-195440 [17]; 2002-226085 [28]  
DOC. NO. NON-CPI: N2002-091167  
DOC. NO. CPI: C2002-037169  
TITLE: Coated stent for implantation in human vessels for treating occlusion in heart and kidney diseases, comprises calcium channel blocker carrying biodegradable **carrier** material coated on stent superstructure.  
DERWENT CLASS: B05 D22 P32  
INVENTOR(S): EASTERLING, W J  
PATENT ASSIGNEE(S): (EAST-I) EASTERLING W J  
COUNTRY COUNT: 1  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002004678	A1	20020110	(200216)*		3

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002004678	A1 CIP of	US 1998-128103	19980803
	CIP of	US 2000-514796	20000228
		US 2001-839572	20010420

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 2002004678	A1 CIP of	US 6031005

PRIORITY APPLN. INFO: US 2001-839572 20010420; US 1998-128103  
19980803; US 2000-514796 20000228

AN 2002-121537 [16] WPIDS  
CR 2000-195440 [17]; 2002-226085 [28]  
AB US2002004678 A UPAB: 20020502

NOVELTY - A coated stent for implantation in human vessels, orifices and conduits for creating and sustaining openings and for preventing re-occlusion of the openings after implantation, comprises a stent superstructure, a biodegradable **carrier** material for coating the stent superstructure, and a calcium channel blocker agent carried by biodegradable **carrier** material.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method for providing a re-occlusion resistant stent implantation to a human patient. The method involves selecting coated stent, and implanting into a human vessel, orifice or conduit.

ACTIVITY - Cardiant.

MECHANISM OF ACTION - Calcium channel blocker.

USE - For surgical implantation of stents, in treatment of arterial occlusion in heart disease, and ureteral occlusion in kidney disease or injury, for creating and sustaining opening, and for preventing re-occlusion of openings after implantation of the stent.

ADVANTAGE - The stent coated with a slow-release calcium channel blocker, interrupts the accumulation or deposition of fibrotic tissue, prevents or, at least, minimizes, processes leading to re-occlusion of the vessel or conduit, after implantation of the stent.

Dwg.0/0

L6 ANSWER 12 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
ACCESSION NUMBER: 2002-075043 [10] WPIDS  
DOC. NO. CPI: C2002-022287  
TITLE: Pharmaceutical pellet useful for inducing or maintaining sleep comprises homogenous mixture of rapidly acting hypnotic agent salt and pellet forming **carrier**.  
DERWENT CLASS: B02  
INVENTOR(S): LEMMENS, J M; PLATTEEUW, J J; VAN DALEN, F; VAN DEN HEUVEL, D J M  
PATENT ASSIGNEE(S): (SYNT-N) SYNTHON BV  
COUNTRY COUNT: 95  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001078725	A2	20011025	(200210)*	EN	41
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001050661	A	20011030	(200219)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001078725	A2	WO 2001-NL299	20010412
AU 2001050661	A	AU 2001-50661	20010412

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001050661	A Based on	WO 200178725

PRIORITY APPLN. INFO: US 2000-196939P 20000413

AN 2002-075043 [10] WPIDS

AB WO 200178725 A UPAB: 20020213

NOVELTY - Pharmaceutical pellet comprises a homogenous mixture of rapidly acting hypnotic agent or its salt and pellet forming **carrier**. The pellet exhibits a specific dissolution profile under US Pharmacopoeia XXIII, Dissolution method I, in a basket apparatus at 37 deg. C in hydrochloric acid medium (0.01N) and at 100 r.p.m.

DETAILED DESCRIPTION - Pharmaceutical pellet comprises a homogenous mixture of rapidly acting hypnotic agent or its salt and pellet forming **carrier**. The pellet exhibits a dissolution profile under US

Pharmacopoeia XXIII, Dissolution method I, in a basket apparatus at 37degreesC in hydrochloric acid medium (0.01N) and at 100 r.p.m that includes 60% of the hypnotic agent being released from the pellet not earlier than 5 minutes from the start of the test.

An INDEPENDENT CLAIM is included for production of spherical pellets which comprises:

(1) combining a solvent (preferably water), a pharmaceutically active agent and/or its salt, and at least one pellet forming **carrier** to form a wet mixture;

(2) stirring and/or chopping the wet mixture to form monolithic, spherical wet pellets, and

(3) drying the wet pellets to form the pellets.

1) 2) 3) The solvent is wet combined by spraying.

ACTIVITY - Antiparkinsonian; Hypnotic.

MECHANISM OF ACTION - None given in source material.

USE - In a pharmaceutical unit dosage form for inducing or maintaining sleep or treating sleep disorders e.g. Parkinson's disease, parkinsonian syndromes and other disorders treatable by zolpidem.

ADVANTAGE - The pellet exhibits a modified release profile. The composition moderates the rapid release occurring in the commercial tablets so that initial over concentration of active agent in body fluids is minimized and the hypnotic action is reasonably delayed to overcome a shortage of sleep. A single dose of the pellet contains a lower amount of the active substance in comparison with that in the commercially available immediate release dosage form due to the advantageous release rates and consequently due to the expected advantageous blood plasma concentration profile which maintains the necessary concentration of zolpidem more effectively. Potential side effects of the hypnotic agent is decreased.  
Dwg.0/4

L6 ANSWER 13 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
ACCESSION NUMBER: 2002-062005 [08] WPIDS  
DOC. NO. CPI: C2002-017651  
TITLE: Composition comprises a carboxyalkylether and an antihypertensive agent for the treatment of hypertension and cardiovascular disorders.  
DERWENT CLASS: B05  
INVENTOR(S): AUERBACH, B J; HITCHCOCK, K D; RYAN, M J  
PATENT ASSIGNEE(S): (WARN) WARNER LAMBERT CO  
COUNTRY COUNT: 86  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
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WO 2001080847	A2	20011101	(200208)*	EN	38
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ					
NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AU BA BB BG BR BZ CA CN CO CR CU CZ DM DZ EE GD GE HR HU					
ID IL IN IS JP KP KR LC LK LR LT LV MA MG MK MN MX MZ NO NZ PL RO					
SG SI SK SL TR TT UA US UZ VN YU ZA					
AU 2001047658	A	20011107	(200219)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
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WO 2001080847	A2	WO 2001-US9088	20010322
AU 2001047658	A	AU 2001-47658	20010322

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001047658	A Based on	WO 200180847

PRIORITY APPLN. INFO: US 2000-242280P 20001020; US 2000-199855P  
20000426

AN 2002-062005 [08] WPIDS

AB WO 200180847 A UPAB: 20020204

NOVELTY - Composition (A) comprises a carboxyalkylether or its addition salt, an antihypertensive agent or its salt and a **carrier** or diluent.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a first composition comprising an antihypertensive agent or its salt, for use with a second composition comprising a carboxyalkylether or its salt, for achieving an antihypertensive and/or cardiovascular effect in a mammal and which shows a synergistic effect;

(2) a first composition comprising an carboxyalkylether or its salt, for use with a second composition comprising an antihypertensive agent or its salt, for managing cardiac risk in a mammal suffering an adverse cardiac event and which shows a synergistic effect;

(3) a first composition comprising an carboxyalkylether of formula (II) or its salt, for use with a second composition comprising an antihypertensive agent or its salt, for achieving an antihypertensive effect in a mammal suffering from hypertension and which shows a synergistic effect;

(4) a kit for achieving a therapeutic effect in a mammal comprising a carboxyalkylether or acid addition salt in a first unit dosage form, an antihypertensive agent or its salt in a second dosage form and a container for the first and second dosage forms;

(5) a method for treating hypertension comprising administering a compound of formula (I), (II) or 6,6'-oxybis(2,2-dimethylhexanoic acid) or their salts, preferably 6,6'-oxybis(2,2-dimethylhexanoic acid) monocalcium; and

(6) a method for preventing a stroke in a mammal comprising administering 6,6'-oxybis(2,2-dimethylhexanoic acid monocalcium.

n, m = 2-9;

R1-R4 = 1-6C alkyl, 1-6C alkenyl, 2-6C alkynyl; or

R1 + R2 + C and R3 + R3 + C = form carbocyclic ring with 3-6 carbons.

ACTIVITY - Hypotensive; Cardiant; Antiarteriosclerotic; Antianginal; Cerebroprotective.

The antihypertensive effects of the carboxyalkylether compound 6,6'-oxybis(2,2-dimethylhexanoic acid) (CI-1027) alone and in combination with the antihypertensive agent quinapril (CI-906) were evaluated in male spontaneously hypertensive rats. CI-1027 monotherapy demonstrated a modest antihypertensive activity. Multiple day quinapril treatment when added to ongoing CI-1027 treatment was found to greatly potentate the antihypertensive response.

MECHANISM OF ACTION - ACE inhibitors; Calcium channel blockers; Angiotension-II receptor antagonists; beta -adrenergic receptor blockers; alpha -adrenergic receptor blockers.

USE - For the treatment of vascular diseases and preventing a stroke in mammals. (A) is used for treating hypertension, angina pectoris, cardiac risk, atherosclerosis, preferably slowing the progression of atheroplaques in the coronary arteries, carotid arteries or peripheral arterial system or causes regression of arterioscleroticplaques in coronary arteries (all claimed).

ADVANTAGE - The combination of the carboxyalkylether and the antihypertensive agent is synergistic.



Dwg.0/0

L6 ANSWER 14 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
 ACCESSION NUMBER: 2001-648522 [74] WPIDS  
 DOC. NO. CPI: C2001-191411  
 TITLE: Treatment of normotensive animals with renal disease  
 comprises use of calcium channel blockers optionally in  
 the presence of a different hypotensive agent.  
 DERWENT CLASS: B03 B05 C02 C03  
 INVENTOR(S): FOSTER, A P  
 PATENT ASSIGNEE(S): (FOST-I) FOSTER A P; (PFIZ) PFIZER INC; (PFIZ) PFIZER LTD  
 COUNTRY COUNT: 95  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001074390	A2	20011011	(200174)*	EN	19
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
US 2001036954	A1	20011101	(200174)		
AU 2001039510	A	20011015	(200209)		

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001074390	A2	WO 2001-IB518	20010328
US 2001036954	A1 Provisional	US 2000-198415P	20000419
		US 2001-818403	20010327
AU 2001039510	A	AU 2001-39510	20010328

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001039510	A Based on	WO 200174390

PRIORITY APPLN. INFO: GB 2000-8332 20000404

AN 2001-648522 [74] WPIDS

AB WO 200174390 A UPAB: 20011217

NOVELTY - Use of calcium channel blockers optionally in the presence of a  
 different class of hypotensive agent e.g. an agent that reduces the effect  
 of endothelin and/or angiotensin to treat normotensive animals with renal  
 disease is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) unit dosage forms comprising 0.1-0.4 mg or 0.8-1.5 mg

**amlodipine**, an optional antihypertensive agent and a  
 pharmaceutical/veterinary **carrier**, diluent or adjuvant; and

(2) a pack comprising unit dose (1) and instructions for the  
 treatment of renal disease in normotensive animals.

ACTIVITY - Hypotensive; Nephrotropic.

Domesticated cats with normotensive chronic renal failure were  
 treated with oral placebo or **amlodipine** (0.125-0.25 mg/kg/day).  
 In the control group (10 cats), the mean glomerular filtration rate (GFR)  
 decreased from 0.9 to 0.75 ml/minute/kg between 7 and 224 days post regime  
 commencement. In the **amlodipine** group (10 cats) the GFR

increased from 0.76 to 0.83 ml/minute/kg over the same period.

MECHANISM OF ACTION - Calcium Channel blocker.

USE - Useful for treating renal diseases in normotensive animals, especially humans and companion animals e.g. dog, horse and domestic cat.

ADVANTAGE - Useful for all normotensive renal conditions.

Dwg.0/0

L6 ANSWER 15 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
 ACCESSION NUMBER: 2001-391763 [42] WPIDS  
 DOC. NO. CPI: C2001-119392  
 TITLE: Pharmaceutical compositions, useful for treating diabetic complications, comprise aldose reductase inhibitor and non-ACE inhibiting anti-hypertensive agent.  
 DERWENT CLASS: B05  
 INVENTOR(S): MYLARI, B L  
 PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC  
 COUNTRY COUNT: 29  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 1106210	A2	20010613	(200142)*	EN	13
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
CA 2327575	A1	20010607	(200145)	EN	
BR 2000005765	A	20010717	(200146)		
JP 2001163805	A	20010619	(200150)		15

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1106210	A2	EP 2000-310719	20001201
CA 2327575	A1	CA 2000-2327575	20001205
BR 2000005765	A	BR 2000-5765	20001207
JP 2001163805	A	JP 2000-369434	20001205

PRIORITY APPLN. INFO: US 1999-169380P 19991207

AN 2001-391763 [42] WPIDS

AB EP 1106210 A UPAB: 20010726

NOVELTY - Pharmaceutical compositions comprising an aldose reductase inhibitor and a non ACE inhibitor anti-hypertensive agent are new.

DETAILED DESCRIPTION - Pharmaceutical compositions comprise:

(1) an aldose reductase inhibitor (ARI) (I), its prodrug or pharmaceutical salt;

(2) a non ACE inhibitor anti-hypertensive agent (II) its prodrug or pharmaceutical salt; and

(3) a **carrier**, vehicle or diluent (III).

An INDEPENDENT CLAIM is also included for a kit comprising dosage forms of (I) and (III), (II) and (III) and a container.

ACTIVITY - Anti-hypertensive; diuretic; vasodilator; anti-diabetic.

MECHANISM OF ACTION - Aldose reductase inhibitors; calcium channel blockers; angiotensin II receptor antagonists; beta adrenoceptor antagonists; neutral endopeptidase inhibitors; alpha adrenoceptor antagonists.

USE - Useful for treating or preventing diabetic complications including neuropathy, nephropathy, cardiomyopathy, retinopathy, cataracts and myocardial infarction.

Dwg.0/0

L6 ANSWER 16 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
 ACCESSION NUMBER: 2000-147185 [13] WPIDS  
 DOC. NO. CPI: C2000-046042  
 TITLE: Nitrate salts of antihypertensive agents.  
 DERWENT CLASS: B02 B03  
 INVENTOR(S): DEL SOLDATO, P; DEL, S P  
 PATENT ASSIGNEE(S): (NICO-N) NICOX SA  
 COUNTRY COUNT: 75  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9967231	A1	19991229	(200013)*	EN	77
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL					
OA PT SD SE SL SZ UG ZW					
W: AL AU BA BB BG BR CA CN CU CZ EE GE HR HU IL IN IS JP KP KR LK LR					
LT LV MG MK MN MX NO NZ PL RO RU SG SI SK TR TT UA US UZ VN YU ZA					
AU 9945139	A	20000110	(200025)		
EP 1087953	A1	20010404	(200120)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LT NL PT RO SE SI					
BR 9911305	A	20011023	(200172)		
CN 1315945	A	20011003	(200205)		
IT 1301759	B	20000707	(200212)		
HU 2001002719	A2	20011228	(200216)		
KR 2001093631	A	20011029	(200223)		

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9967231	A1	WO 1999-EP4138	19990615
AU 9945139	A	AU 1999-45139	19990615
EP 1087953	A1	EP 1999-927990	19990615
		WO 1999-EP4138	19990615
BR 9911305	A	BR 1999-11305	19990615
		WO 1999-EP4138	19990615
CN 1315945	A	CN 1999-807516	19990615
IT 1301759	B	IT 1998-MI1408	19980619
HU 2001002719	A2	WO 1999-EP4138	19990615
		HU 2001-2719	19990615
KR 2001093631	A	KR 2000-714179	20001214

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9945139	A Based on	WO 9967231
EP 1087953	A1 Based on	WO 9967231
BR 9911305	A Based on	WO 9967231
HU 2001002719	A2 Based on	WO 9967231

PRIORITY APPLN. INFO: IT 1998-MI1408 19980619

AN 2000-147185 [13] WPIDS

AB WO 9967231 A UPAB: 20000313

NOVELTY - The nitrate salts of compounds with antihypertensive activity provide an improved therapeutic profile, and fewer side effects compared to known antihypertensive agents.

DETAILED DESCRIPTION - The nitrate salts of many antihypertensive agents are new. The agents include compounds of the following general

formulae:

XA1 = -COOH,

RA1 = -CH<sub>2</sub>OH,

The agents include Valsartan, Hydralazine, Minoxidil, Sildenafil, Zaprinas, Terazosin, Prazosin, Bucindolol, Bepridil, Clentiazem, Diltiazem, Fendiline, Gallopamil, Mibefradil, Prenylamine, Semotiadil, Terodiline, Verapamil, **Amlodipine**, Aranidipine, Barnidipine, Benedipine, Cilnidipine, Efonidipine, Elgodipine, Felodipine, Isradipine, Lacidipine, Lercanidipine, Manidipine, Nicardipine, Nifedipine, Nilvadipine, Nimodipine, Nisoldipine, Nitrendipine, Cinnarizine, Flunarizine, Lidoflazine, Lomerizine, Bencyclane, Etafenone, Fantofarone, Althiazide, Bendroflumethiazide, Benthiazide, Benzylhydrochlorothiazide, Buthiazide, Chlorothiazide, Chlortalidone, Cyclopenthiazide, Cyclothiazide, Epithiazide, Ethiazide, Fenquizone, Indapamide, Hydrochlorthiazide, Hydroflumethiazide, Methyclothiazide, Methycrane, Metolazone, Paraflutizide, Polythiazide, Quinethazone, Teclothiazide, Trichlormethiazide, Protheobromine, Teobromine, Aminometradine, Amisotradine, Amanozine, Amiloride, Chlorazanyl, Etozolin, Hydracarbazine, Muzolimine, Perhexiline, Triamterene, Bumetanide, Furosemide, Torasemide and Apomorphine, and analogues.

ACTIVITY - Antihypertensive.

MECHANISM OF ACTION - None given.

USE - For treating hypertension and cardiovascular disease (claimed).

ADVANTAGE - In many cases, the nitrate salt had greater antihypertensive effects and fewer side effects than its precursor. E.g. the effects on vasoconstriction in rats were: **Carrier** 100%, Sildenafil nitrate 25% and Sildenafil 68%; the arterial pressures in rats were: **Carrier** 170, Losartan nitrate 115, and Losartan 153 mm Hg; the incidences of gastric toxicity were: Control 50, Sildenafil 100; Sildenafil nitrate 20%.  
Dwg.0/0

L6 ANSWER 17 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
ACCESSION NUMBER: 2000-064417 [06] WPIDS  
DOC. NO. NON-CPI: N2000-050529  
DOC. NO. CPI: C2000-018073  
TITLE: Synergistic composition for treatment of arrhythmia, especially in patients with arterial fibrillation.  
DERWENT CLASS: B03 B05 P34  
INVENTOR(S): BILLING, C B; FALK, R H; FRIEDRICH, T  
PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC; (UYBO-N) UNIV BOSTON  
COUNTRY COUNT: 28  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 965341	A2	19991222	(200006)*	EN	12
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 11335278	A	19991207	(200008)		10
CA 2270022	A1	19991114	(200017)	EN	
MX 9904460	A1	20000701	(200134)		

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 965341	A2	EP 1999-303489	19990504
JP 11335278	A	JP 1999-132173	19990513
CA 2270022	A1	CA 1999-2270022	19990427

MX 9904460 A1

MX 1999-4460

19990513

PRIORITY APPLN. INFO: US 1998-85496P 19980514

AN 2000-064417 [06] WPIDS

AB EP 965341 A UPAB: 20000203

NOVELTY - A pharmaceutical composition comprises:

(a) dofetilide (N-(4-(2-((2-(4-methanesulfonylamino-phenoxy)-ethyl)-methyl-amino)-ethyl)-phenyl) -methanesulfonamide);

(b) a calcium channel blocker; and

(c) a diluent or **carrier**.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a kit comprising

(a) dofetilide and a **carrier** in a unit dosage;(b) a calcium channel blocker and a **carrier** in a unit dosage; and

(c) a container for the dosage forms.

ACTIVITY - Antiarrhythmic.

Recurrence rate of arterial fibrillation was analyzed in a group of 264 patients. Patients dosed with the above combination showed reduced risk of recurrence (48 % cf. 38.1 %).

MECHANISM OF ACTION - Calcium channel blocker. Dofetilide is a selective inhibitor of the rapid component of the delayed rectifier potassium current which prolongs the action potential duration and the effective refractory period.

USE - Treatment of arrhythmia, especially in patients with arterial fibrillation, and with normal sinus rhythm maintained; or whose electrical remodeling of the atrium is inhibited prior to conversion to sinus rhythm; or who have been pre-treated with **amlodipine** prior to conversion to normal sinus rhythm with dofetilide and optional electrocardioversion to result in inhibition of recurrence of arterial fibrillation post cardioversion (all claimed).ADVANTAGE - The quantities of dofetilide and **amlodipine** in the composition are insufficient alone for treatment of arrhythmia, however in combination a synergistic effect is achieved.  
Dwg.0/0

L6 ANSWER 18 OF 22 WPIDS (C) 2002 THOMSON DERWENT

ACCESSION NUMBER: 1999-214611 [18] WPIDS

DOC. NO. CPI: C1999-063222

TITLE: Use of a synergistic combination of **amlodipine** and a statin compound for treating angina pectoris and atherosclerosis.

DERWENT CLASS: B03

INVENTOR(S): BUCH, J; SCOTT, R A D

PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC; (PFIZ) PFIZER INC

COUNTRY COUNT: 84

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9911263	A1	19990311	(199918)*	EN	55
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL					
OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE					
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG					
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG					
US UZ VN YU ZW					
AU 9884585	A	19990322	(199931)		
ZA 9807843	A	20000426	(200027)		55

NO 2000000999 A 20000228 (200029)  
 EP 1003507 A1 20000531 (200031) EN  
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MK NL PT RO  
 SE SI  
 CZ 2000000319 A3 20000816 (200048)  
 BR 9811558 A 20000822 (200050)  
 SK 2000000139 A3 20000814 (200051)  
 CN 1268054 A 20000927 (200067)  
 HU 2000003103 A2 20010131 (200118)  
 MX 2000002085 A1 20001001 (200158)  
 KR 2001022385 A 20010315 (200159)  
 JP 2001514224 W 20010911 (200167) 61  
 US 2002025981 A1 20020228 (200220)  
 AU 744982 B 20020307 (200229)

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9911263	A1	WO 1998-IB1220	19980810
AU 9884585	A	AU 1998-84585	19980810
ZA 9807843	A	ZA 1998-7843	19980828
NO 2000000999	A	WO 1998-IB1220	19980810
		NO 2000-999	20000228
EP 1003507	A1	EP 1998-935246	19980810
		WO 1998-IB1220	19980810
CZ 2000000319	A3	WO 1998-IB1220	19980810
		CZ 2000-319	19980810
BR 9811558	A	BR 1998-11558	19980810
		WO 1998-IB1220	19980810
SK 2000000139	A3	WO 1998-IB1220	19980810
		SK 2000-139	19980810
CN 1268054	A	CN 1998-808465	19980810
HU 2000003103	A2	WO 1998-IB1220	19980810
		HU 2000-3103	19980810
MX 2000002085	A1	MX 2000-2085	20000228
KR 2001022385	A	KR 2000-700964	20000128
JP 2001514224	W	WO 1998-IB1220	19980810
		JP 2000-508366	19980810
US 2002025981	A1	US 1997-57555P	19970829
	Provisional	US 2000-513889	20000225
	Cont of	US 2001-975765	20011010
AU 744982	B	AU 1998-84585	19980810

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9884585	A Based on	WO 9911263
EP 1003507	A1 Based on	WO 9911263
CZ 2000000319	A3 Based on	WO 9911263
BR 9811558	A Based on	WO 9911263
HU 2000003103	A2 Based on	WO 9911263
JP 2001514224	W Based on	WO 9911263
AU 744982	B Previous Publ. Based on	AU 9884585 WO 9911263

PRIORITY APPLN. INFO: US 1997-57555P 19970829  
 AN 1999-214611 [18] WPIDS  
 AB WO 9911263 A UPAB: 20011203

NOVELTY - Use of a synergistic combination of amlodipin (I) and a statin (II) compound produces a synergistic antihypertensive, hypolipidemic, antianginal or antiatherosclerotic effect.

DETAILED DESCRIPTION - A composition comprises:

- (a) (I) (disclosed in US 4,572,909) or a salt;
- (b) (II) (not atorvastatin) or a salt; and
- (c) a **carrier** or diluent.

INDEPENDENT CLAIMS are included for the following:

- (i) separate compositions of (I) and (II) for use together
- (ii) a kit comprising (a), (b), (c) in a container.

ACTIVITY - Antihypertensive; hypolipidemic; antianginal; antiatherosclerotic.

MECHANISM OF ACTION - Calcium channel blocker (I); HMG-CoA reductase inhibitor (II).

USE - The combination is useful for treating angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia, and subjects with symptoms of cardiac risk.

ADVANTAGE - The combination of (a) and (b) is synergistic. No suitable data given.  
Dwg.0/0

L6 ANSWER 19 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
ACCESSION NUMBER: 1999-204972 [17] WPIDS  
DOC. NO. CPI: C1999-059655  
TITLE: Use of a synergistic combination of atorvastatin and antihypertensive agent for treating angina pectoris and atherosclerosis.  
DERWENT CLASS: B03 B05  
INVENTOR(S): SCOTT, R A D  
PATENT ASSIGNEE(S): (PFIZ) PFIZER INC  
COUNTRY COUNT: 84  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9911260	A1	19990311	(199917)*	EN	51
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL					
OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE					
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG					
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG					
US UZ VN YU ZW					
AU 9884589	A	19990322	(199931)		
ZA 9807839	A	20000426	(200027)		49
NO 2000000996	A	20000427	(200032)		
EP 1009400	A1	20000621	(200033)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MK NL PT RO					
SE SI					
CZ 2000000342	A3	20000816	(200048)		
BR 9811556	A	20000822	(200050)		
CN 1268053	A	20000927	(200067)		
SK 2000000143	A3	20001211	(200103)		
HU 20000004318	A2	20010528	(200140)		
KR 2001022477	A	20010315	(200159)		
JP 2001514223	W	20010911	(200167)		57
AU 740424	B	20011101	(200175)		
AU 2002014783	A	20020321	(200230)#		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9911260	A1	WO 1998-IB1230	19980811
AU 9884589	A	AU 1998-84589	19980811
ZA 9807839	A	ZA 1998-7839	19980828
NO 2000000996	A	WO 1998-IB1230	19980811
		NO 2000-996	20000228
EP 1009400	A1	EP 1998-935250	19980811
		WO 1998-IB1230	19980811
CZ 2000000342	A3	WO 1998-IB1230	19980811
		CZ 2000-342	19980811
BR 9811556	A	BR 1998-11556	19980811
		WO 1998-IB1230	19980811
CN 1268053	A	CN 1998-808463	19980811
SK 2000000143	A3	WO 1998-IB1230	19980811
		SK 2000-143	19980811
HU 20000004318	A2	WO 1998-IB1230	19980811
		HU 2000-4318	19980811
KR 2001022477	A	KR 2000-701062	20000131
JP 2001514223	W	WO 1998-IB1230	19980811
		JP 2000-508363	19980811
AU 740424	B	AU 1998-84589	19980811
AU 2002014783	A Div ex	AU 1998-84589	19980811
		AU 2002-14783	20020201

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9884589	A Based on	WO 9911260
EP 1009400	A1 Based on	WO 9911260
CZ 2000000342	A3 Based on	WO 9911260
BR 9811556	A Based on	WO 9911260
HU 20000004318	A2 Based on	WO 9911260
JP 2001514223	W Based on	WO 9911260
AU 740424	B Previous Publ.	AU 9884589
	Based on	WO 9911260
AU 2002014783	A Div ex	AU 740424

PRIORITY APPLN. INFO: US 1997-57276P 19970829; AU 2002-14783  
20020201

AN 1999-204972 [17] WPIDS

AB WO 9911260 A UPAB: 20011203

NOVELTY - Use of a combination of atorvastatin and an antihypertensive agent produces a synergistic antihypertensive, hypolipidemic, antianginal or antiatherosclerotic effect.

DETAILED DESCRIPTION - A composition comprises:

- (a) atorvastatin (disclosed in US4681893) or a salt;
- (b) an antihypertensive agent (not **amlodipine**) or a salt;

and

- (c) a **carrier** or diluent.

INDEPENDENT CLAIMS are included for separate compositions of (a) and (b) for use together, and kits containing combinations of (a) and (b).

ACTIVITY - Antihypertensive; hypolipidemic; antianginal; antiatherosclerotic.

MECHANISM OF ACTION - None given.

USE - The combination is useful for treating angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia, and subjects with symptoms of cardiac risk.

ADVANTAGE - The combination of (a) and (b) is synergistic.



Dwg.0/0

L6 ANSWER 20 OF 22 WPIDS (C) 2002 THOMSON DERWENT  
 ACCESSION NUMBER: 1999-204971 [17] WPIDS  
 DOC. NO. CPI: C1999-059654  
 TITLE: Use of a synergistic combination of **amlodipine**  
 and atorvastatin for treating angina pectoris and  
 atherosclerosis.  
 DERWENT CLASS: B03  
 INVENTOR(S): BUCH, J; SCOTT, R A D  
 PATENT ASSIGNEE(S): (PFIZ) PFIZER INC  
 COUNTRY COUNT: 84  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9911259	A1	19990311	(199917)*	EN	50
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9885548	A	19990322	(199931)		
ZA 9807844	A	20000426	(200027)		50
NO 2000000998	A	20000228	(200029)		
EP 1003503	A1	20000531	(200031)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MK NL PT RO SE SI					
CZ 2000000511	A3	20000614	(200037)		
BR 9812030	A	20000926	(200051)		
CN 1268052	A	20000927	(200067)		
SK 2000000204	A3	20001211	(200103)		
HU 2000003656	A2	20010328	(200124)		
KR 2001023498	A	20010326	(200161)		
JP 2001514222	W	20010911	(200167)		65

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9911259	A1	WO 1998-IB1225	19980811
AU 9885548	A	AU 1998-85548	19980811
ZA 9807844	A	ZA 1998-7844	19980828
NO 2000000998	A	WO 1998-IB1225	19980811
		NO 2000-998	20000228
EP 1003503	A1	EP 1998-936587	19980811
		WO 1998-IB1225	19980811
CZ 2000000511	A3	WO 1998-IB1225	19980811
		CZ 2000-511	19980811
BR 9812030	A	BR 1998-12030	19980811
		WO 1998-IB1225	19980811
CN 1268052	A	CN 1998-808460	19980811
SK 2000000204	A3	WO 1998-IB1225	19980811
		SK 2000-204	19980811
HU 2000003656	A2	WO 1998-IB1225	19980811
		HU 2000-3656	19980811
KR 2001023498	A	KR 2000-702144	20000229
JP 2001514222	W	WO 1998-IB1225	19980811
		JP 2000-508362	19980811

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9885548	A Based on	WO 9911259
EP 1003503	A1 Based on	WO 9911259
CZ 2000000511	A3 Based on	WO 9911259
BR 9812030	A Based on	WO 9911259
HU 2000003656	A2 Based on	WO 9911259
JP 2001514222	W Based on	WO 9911259

PRIORITY APPLN. INFO: US 1997-57275P 19970829

AN 1999-204971 [17] WPIDS

AB WO 9911259 A UPAB: 20011203

NOVELTY - Use of a combination of **amlodipine** and atorvastatin produces a synergistic antihypertensive, hypolipidemic, antianginal or antiatherosclerotic effect.

DETAILED DESCRIPTION - A composition comprises:

(a) **amlodipine** (I) (disclosed in US 4,572,909) or a salt;

(b) atorvastatin (II) (disclosed in US 4,681,893) or a salt; and

(c) a **carrier** or diluent.

INDEPENDENT CLAIMS are included for separate compositions of (I) and (II) for use together, and kits containing combinations of (I) and (II).

ACTIVITY - Antihypertensive; hypolipidemic; antianginal; antiatherosclerotic.

MECHANISM OF ACTION - None given.

USE - The combination is useful for treating angina pectoris, atherosclerosis; combined hypertension and hyperlipidemia, and subjects with symptoms of cardiac risk.

ADVANTAGE - The combination of (I) and (II) is synergistic.

Dwg.0/0

L6 ANSWER 21 OF 22 WPIDS (C) 2002 THOMSON DERWENT

ACCESSION NUMBER: 1996-051911 [06] WPIDS

DOC. NO. NON-CPI: N1996-043499

DOC. NO. CPI: C1996-017026

TITLE: Unit dose delivery system for hydrophobic drugs - comprises layers of hydrophilic material over hydrophobic material.

DERWENT CLASS: A96 B07 P33

INVENTOR(S): VERONESI, P A; VERONESI, P

PATENT ASSIGNEE(S): (THER-N) THERAPICON SRL

COUNTRY COUNT: 66

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
GB 2290965	A	19960117	(199606)*		68
WO 9601612	A1	19960125	(199610)	EN	70
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG					
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE					
KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NO NZ PL PT RO RU SD SE					
SG SI SK TJ TM TT UA UG US UZ VN					
AU 9529252	A	19960209	(199619)		
ZA 9505741	A	19970326	(199718)		71
EP 769938	A1	19970502	(199722)	EN	
R: AT BE CH DE ES FR GB GR IE IT LI NL PT SE					
ES 2104522	T1	19971016	(199748)		
JP 10502376	W	19980303	(199819)		47

KR 97704427 A 19970906 (199839)  
 US 5814338 A 19980929 (199846)  
 EP 769938 B1 19981028 (199847) EN  
 R: AT BE CH DE ES FR GB GR IE IT LI NL PT SE  
 DE 69505671 E 19981203 (199903)  
 ES 2104522 T3 19990316 (199918)  
 AU 707076 B 19990701 (199937)

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
GB 2290965	A	GB 1994-13951	19940711
WO 9601612	A1	WO 1995-EP2488	19950624
AU 9529252	A	AU 1995-29252	19950624
ZA 9505741	A	ZA 1995-5741	19950711
EP 769938	A1	EP 1995-924940	19950624
		WO 1995-EP2488	19950624
ES 2104522	T1	EP 1995-924940	19950624
JP 10502376	W	WO 1995-EP2488	19950624
		JP 1996-504081	19950624
KR 97704427	A	WO 1995-EP2488	19950624
		KR 1997-700142	19970110
US 5814338	A	WO 1995-EP2488	19950624
		US 1997-765952	19970109
EP 769938	B1	EP 1995-924940	19950624
		WO 1995-EP2488	19950624
DE 69505671	E	DE 1995-605671	19950624
		EP 1995-924940	19950624
		WO 1995-EP2488	19950624
ES 2104522	T3	EP 1995-924940	19950624
AU 707076	B	AU 1995-29252	19950624

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9529252	A Based on	WO 9601612
EP 769938	A1 Based on	WO 9601612
ES 2104522	T1 Based on	EP 769938
JP 10502376	W Based on	WO 9601612
KR 97704427	A Based on	WO 9601612
US 5814338	A Based on	WO 9601612
EP 769938	B1 Based on	WO 9601612
DE 69505671	E Based on	EP 769938
	Based on	WO 9601612
ES 2104522	T3 Based on	EP 769938
AU 707076	B Previous Publ.	AU 9529252
	Based on	WO 9601612

PRIORITY APPLN. INFO: GB 1994-13951 19940711

AN 1996-051911 [06] WPIDS

AB GB 2290965 A UPAB: 19981028

Unit dosage delivery system (UDS) comprises (a) a capsule housing consisting of two or more couple layers, sheaths or films from different materials, the outer layer or sheath having a hydrophilic character and the inner sheath or films having a hydrophobic character; (b) a filling comprising one or more active hydrophobic drugs opt. with extended drug properties. Also claimed is a medicated compsn. comprising a **carrier** and a unit drug delivery system contg. (i) a capsule

housing comprising: (a1) an outer hydrophilic layer consisting of gelatin, glycerin and/or modified sorbitol soln., water or other suitable cpds. such as polyphenol cpds.; (b1) an inner hydrophobic silicone, silicone mixt. or silicone polymer layer; and (c1) opt. inner third or additional films or sheaths made from silicone polymers or waxes, or jaluronic acid polymers; and (ii) a capsule filling comprising: (a2) one or more drug substances admixed, dissolved, suspended or agglomerated in a hydrophobic support; (b2) silicone resin having a viscosity of 100-110 cSt and a specific gravity of 0.96-1.02; and (c2) opt. release modifying substances providing extended release of the drug selected from beeswax, silicone waxes and natural or modified stearic acid, palmitic acid, myristic acid, lauric acid, stearyl alcohol, cetyl alcohol, glycerol stearate, ethyl oleate, arachids oil, cottonseed oil, rapeseed oil, liq. paraffin or polyethylene glycol (400-200,000).

USE - The capsule contains drugs pref. oligopeptides, peptides, proteins, prostaglandins, cholesterol lowering agents, gastric antiseecretories, antiacids, antiallergic agents, antiasthmatic agents, ACE inhibitors, antineoplastic agents, antiviral nucleoside agents, antiParkinson agents, antiepileptic agents, analgesics, non-steroidal antiinflammatories, antitussives, decongestionants, narcotics, antibiotics, cardiovasculars, their salts, lyophylised yeasts, vitamins or a vaccine, esp. the drug is cholera, typhoid or poliomyelitis vaccine, a calcitonin, erythropoietin, insulin, cyclosporin, lysozyme, tpsin, carboxypeptidase, interleukin-1, prostaglandin A1, E2, F2 a or I2, misoprostol, thromboxane, eicosapentaenoic acid, docosahexanoic acid, omeprazole, lansoprazole, rapitidine, sodium bicarbonate cetirezine, bamiphylline, captopril, enalapril, etoposide, sodium restramustine phosphate, acyclovir, selegiline, lamotrigine, aspirin, piroxicam, ketorolac, nifedipine, **amlodipine**, diltiazem, nicorandil, Lactobacillus bifidus or Lactobacillus bulgaricus.

ADVANTAGE - The UDS gives the drug protection against the atmosphere, oxidation, or moisture induced hydrolytic or degradation processes, allows a capsule filling moisture content <1%, minimises the diffusion of residue water from the external capsule housing to the filling, or of a water soluble active agent to the outer housing, causes unpleasant tastes or odours, controls or improves efficiently the site of action of the drug, prolongs when necessary, the release of the above agent from the filling, and avoids incompatibilities between the drug and auxiliary or optional ingredients. The UDS also allows delicate or unstable drugs to be formulated and delivered, enhances the protective conditions and prolongs the stability of the formulation.

Dwg.0/3

L6 ANSWER 22 OF 22 JAPIO COPYRIGHT 2002 JPO  
 ACCESSION NUMBER: 2000-044475 JAPIO  
 TITLE: SUPPRESSION OF MIGRATION OF SMOOTH MUSCLE CELL BY (R)-  
**AMLODIPINE**  
 INVENTOR: CHAHWALA SURESH BABUBHAI; WINSLOW DEREK PAUL  
 PATENT ASSIGNEE(S): PFIZER INC)  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 2000044475A		20000215	Heisei	A61K031-44

JP

#### APPLICATION INFORMATION

ST19N FORMAT:	JP1994-208778	19940810
ORIGINAL:	JP11208778	Heisei
PRIORITY APPLN. INFO.:	GB1993 9317773	19930826

SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined  
Applications, Vol. 2000

AN 2000-044475 JAPIO

AB PROBLEM TO BE SOLVED: To obtain a composition capable of greatly suppressing the migration of smooth muscle cells in spite of practically showing no calcium channel blocking activity, and useful for the treatment of e.g. atherosclerosis by including an R(+) isomer of **amlodipine**, a **carrier** and so on.

SOLUTION: This composition is obtained by including (A) an R(+) isomer of **amlodipine** or a pharmacologically permissible salt thereof and (B) a pharmacologically permissible **carrier** or diluent. In the case of a preparation for oral administration, the component A is pref. included at 1-100 mg. In the case of a preparation for intravenous administration, the component A is pref. included at 1-20 mg. This composition is useful for the treatment e.g. of early recurrent stenosis post angioplasty and endometriosis.

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